

DRAFT TRANSLATION from
RISEING SUN COMMUNICATIONS LTD.

(Incorporating Rotha Fullford Leopold of Canberra, Australia)

40 Bowling Green Lane, London EC1R 0NE

JAPANESE PATENT APPLICATION

No. J57-021320

A HYPOGLYCEMIC AGENT

(21) Filing no.: 55-93853

(22) Filing date: July 11, 1980.

(43) Specification published: February 4, 1982.

(72) Inventor(s): Narumitsu HONDA
c/o Chugai Pharmaceutical General Laboratories.
3-41-8, Takada, Toshima-ku, Tokyo.
Hideaki NAGAI
c/o Chugai Pharmaceutical General Laboratories.
3-41-8, Takada, Toshima-ku, Tokyo.
Masuo KOIZUMI
c/o Chugai Pharmaceutical General Laboratories.
3-41-8, Takada, Toshima-ku, Tokyo.
Yasushi MURAKAMI
c/o Chugai Pharmaceutical General Laboratories.
3-41-8, Takada, Toshima-ku, Tokyo.
Hideki NAKANO
c/o Chugai Pharmaceutical General Laboratories.
3-41-8, Takada, Toshima-ku, Tokyo.
(71) Assignee(s): Chugai Pharmaceutical KK.
5-5-1 Ukima, Kita-ku, Tokyo.

Examination request: not yet made

Number of Invention: 1

(Total 4 pages)

(51) Int.Cl. ³	Identification Code	JPO classification
A61K 31/13	ADP	6408-4C
31/165		6408-4C

Please Note- Names of Japanese firms, research laboratories and government entities, as translated are not necessarily identical with the names adopted by such organisations for international contacts. Japanese personal and surnames often permit of several readings and the ones used in this translation are not necessarily the ones preferred by their bearers. Foreign names mentioned in Japanese specifications cannot always be accurately reconstructed.

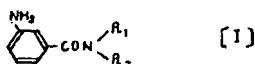
Specification

1. Title of Invention

A hypoglycemic agent.

2. Patent Claims

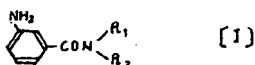
A hypoglycemic agent containing as effective component a compound represented by general formula



(wherein, R₁ and R₂ may be the same or different and denote a hydrogen atom, a straight-chain, branched-chain or cyclic alkyl group, an aralkyl group which can have a substituent in the nucleus, or a phenyl group which may be substituted).

3. Detailed explanation of the invention

This invention is a hypoglycemic agent containing as effective component a compound represented by general formula



(wherein, R₁ and R₂ may be the same or different and denote a hydrogen atom, a straight-chain, branched-chain or cyclic alkyl group, an aralkyl group which can have a substituent in the nucleus, or a phenyl group which may be substituted).

Among the compounds represented by aforesaid formula [I], a well known compounds are included, however, hypoglycemic action or a pharmacological action that suggests this are not described whatsoever in the prior publications describing those compounds.

The compounds represented by aforesaid formula [I] can be easily obtained for example by reduction by conventional method of corresponding meta-nitrobenzoic acid amide species as shown in the Reference Example below.

Reference Example

Into a mixed solution of 6 g isopropylamine, 15 ml triethylamine and 200 ml acetone was gradually added 18.6 g meta-nitrobenzoyl chloride under ice cooling and stirring. the mixture was stirred at the same temperature for 30 minutes and then at room temperature for one hour, thereafter, the reaction liquor was discharged into 1 litre of water, precipitated crystals were recovered by

filtration, washed with water, thereafter recrystallised, and meta-nitro-N-isopropylbenzamide (m.p. 131-132°C) 18.7 g was thereby obtained as colourless acicular crystals. Hydrogen was passed through a mixed liquor of 5.2 g of said amide, 0.5 g of 10 % palladium-carbon and 100 ml ethanol, and catalytic reduction was carried out by conventional method. After theoretical quantity hydrogen was absorbed, catalyst was eliminated, the reaction liquor was concentrated under reduced pressure, the residue was recrystallised from ethanol, and thereby meta-amino-N-isopropyl benzamide (compound 1) 4.1 g was obtained as colourless acicular crystals. m.p. 148-149°C.

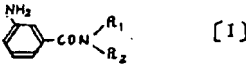
Elemental analysis: as molecular formula $C_{10}H_{14}N_2O$




	C	H	N
Calculated values (%)	67.38	7.92	15.72
Measured values (%)	67.35	7.94	15.69













Compounds of Table 1 were obtained in the same way as above.


wherein, compounds 25, 27 and 29 were obtained as oily substances, the value of high mass spectra are shown in the Table and the NMR values are shown below the Table.

Table 1



Comp. No.	Substituent and position		Molecular formula	m.p. (°C)	Yield (%)	Elemental analysis value					
	R ₁	R ₂				Calc. (%)			Measured (%)		
						C	H	N	C	H	N
2	H	H	C ₇ H ₉ N ₂ O	77~78	81	61.75	5.92	20.58	61.71	5.98	20.55
3	"	CH ₃	C ₈ H ₁₀ N ₂ O	121~122	85	63.98	6.71	18.65	63.92	6.68	18.69
4	"	C ₂ H ₅	C ₉ H ₁₃ N ₂ O	70~71	76	65.83	7.37	17.06	65.72	7.28	17.19
5	"	n-C ₃ H ₇	C ₁₀ H ₁₅ N ₂ O	57~58	78	67.38	7.92	15.72	67.25	7.88	15.64
6	"	n-C ₄ H ₉	C ₁₁ H ₁₈ N ₂ O	112~113	75	68.72	8.39	14.57	68.70	8.37	14.50
7	"	sec-C ₄ H ₉	"	109~111	74	"	"	"	68.67	8.44	14.65
8	"	1-C ₄ H ₉	"	126~127	79	"	"	"	68.69	8.36	14.51
9	"	4-C ₄ H ₉	"	87~89	78	"	"	"	68.75	8.46	14.62
10	"		C ₁₃ H ₁₃ N ₂ O	147~148	84	71.52	8.31	12.83	71.58	8.35	12.76
11	"		C ₁₃ H ₁₃ N ₂ O	132~133	86	73.56	5.70	13.20	73.50	5.67	13.26
12	"		C ₁₄ H ₁₅ N ₂ O	88~89	84	74.31	6.24	12.38	74.24	6.20	13.45

Comp. No.	Substituent and position		Molecular formula	m.p. (°C)	Yield (%)	Elemental analysis value					
	R ₁	R ₂				Calc. (%)			Measured (%)		
						C	H	N	C	H	N
13	H		C ₁₈ H ₁₆ N ₂ O ₂	83~84	76	66.16	5.92	10.29	65.98	5.88	10.35
14	"		C ₁₄ H ₁₂ N ₂ O ₂	180~182	58	63.87	5.13	16.46	65.75	5.18	16.56
15	"		"	135~136	59	"	"	"	65.79	5.10	16.52
16	"		"	223~226	68	"	"	"	65.81	5.07	16.53
17	"		C ₁₃ H ₁₂ N ₂ O	151~153	79	68.70	5.77	18.49	68.64	5.79	18.43
18	"		"	130~131	71	"	"	"	68.77	5.70	18.53
19	"		"	150~151	74	"	"	"	68.75	5.67	18.42
20	"		C ₁₄ H ₁₂ N ₂ O ₂	231~233	59	65.62	4.72	10.93	65.71	4.66	11.02
21	"		C ₁₄ H ₁₄ N ₂ O	96~97	73	74.31	6.24	12.38	74.25	6.19	12.49
22	"		C ₁₈ H ₁₆ N ₂ O	94~95	80	74.97	6.71	11.66	74.92	6.75	11.61
23	"		C ₁₈ H ₁₈ N ₂ O ₂	109~110	79	70.29	6.29	10.93	70.34	6.32	10.89
24	"		C ₁₄ H ₁₂ ON ₂ O	131~132	67	64.49	5.03	10.75	64.42	5.00	10.79

Comp. No.	Substituent and position		Molecular formula	m.p. (°C)	Yield (%)	Elemental analysis value					
	R ₁	R ₂				Calc. (%)			Measured (%)		
						C	H	N	C	H	N
25	H		C ₁₅ H ₁₅ N ₂ O	oil	82	ハイマススペクトル 240.1259			(#1) 240.1246		
26	OH ₃	OH ₃	C ₉ H ₁₂ N ₂ O	87~88	82	65.83	7.37	17.06	65.78	7.41	17.12
27	<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	C ₁₅ H ₂₀ N ₂ O	oil	76	ハイマススペクトル 220.1571			(#2) 220.1580		
28	<i>i</i> -C ₃ H ₇	<i>i</i> -C ₃ H ₇	"	179~180	80	70.87	9.15	12.72	70.79	9.15	12.78
29	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	C ₁₅ H ₂₄ N ₂ O	oil	74	ハイマススペクトル 248.1883			(#3) 248.1875		
30	<i>i</i> -C ₄ H ₉	<i>i</i> -C ₄ H ₉	"	85~86	79	72.54	9.74	11.28	72.48	9.79	11.34

#1 : NMR (CDCl₃) δ : 7.55~6.40 (10H, aromatic-H, -CONH-), 3.75 (2H, s, -NH₂), 3.45 (2H, t, J=6Hz, -OH₂-), 2.75 (2H, t, J=6Hz, -OH₂-)

#2 : NMR (ODCl₃) δ : 7.35~6.50 (4H, aromatic-H), 3.90 (2H, s, -NH₂), 3.30 (4H, t, J=6Hz, (-CH₂CH₂CH₂)×2), 1.60 (4H, sextet, J=6Hz, (-CH₂CH₂CH₂)×2), 0.85 (6H, t, J=6Hz, (-CH₂CH₂CH₂)×2)

#3 : NMR (ODCl₃) δ : 7.15~6.40 (4H, aromatic-H), 4.00 (2H, s, -NH₂), 3.30 (4H, br, (-CH₂CH₂CH₂CH₂)×2), 1.40 (8H, br, (-CH₂CH₂CH₂CH₂)×2), 0.90 (6H, br, (-CH₂CH₂CH₂CH₂)×2)

The compounds of this invention obtained in this way have excellent insulin biosynthesis promotion action and hypoglycemic action, and are useful at 0.1-100 mg/kg with respect to human, and the effect thereof can be sustained for 24 hours or more by the administration of 0.1-100 mg/kg once a day.

For administration, preparations formed into desired agent form by conventional means used for normal formulation method are used.

Example 1

5-week-old DDY mice (males, body weight 25-30 g) comprising 5 animals per group were fasted for 16 hours, thereafter, aqueous solution or suspension of compounds of this invention (200 mg/kg) was orally administered, and 20 minutes later, streptozotocin 200 mg/kg was intravenously administered. Blood was collected from the heart on 24 hours later, blood sugar quantity was measured by glucose oxidase method and the plasma insulin quantity was measured by two antibody method. The measurement results are shown in Table 2.

Wherein, the compound number in the Table corresponds to the compound number of Reference Example.

Table 2

Administered compound	Blood glucose (mg/dl) mean \pm S.E.M.	Plasma Insulin (μ U/ml) mean \pm S.E.M.
Normal mouse	157 \pm 6	199 \pm 40
None (control)	386 \pm 21	43 \pm 25
1	224 \pm 19 ***	176 \pm 37 *
2	157 \pm 16 ***	153 \pm 46
3	260 \pm 33 *	213 \pm 48 *
4	248 \pm 47 *	192 \pm 54
10	263 \pm 36 *	201 \pm 38 *
12	265 \pm 32 *	253 \pm 56 *
18	166 \pm 35 ***	190 \pm 51 *
21	150 \pm 6 ***	224 \pm 30 ***
24	193 \pm 41 **	173 \pm 63
25	210 \pm 39 **	184 \pm 48 *
26	267 \pm 53	220 \pm 37 **

*, P < 0.05, **, P < 0.01, ***, P < 0.001

Example 2

meta-aminobenzamide (compound 2)	100 pts.
calcium hydrogenphosphate	58.5 pts.
crystalline cellulose	50 pts.
corn starch	40 pts.
calcium stearate	1.5 pts.

Above components were thoroughly mixed, and tablets, 250 mg per tablet (containing 100 mg effective component) was formed by conventional method. This is used as a hypoglycemic agent.

Example 3

A 40 % aqueous solution of meta-aminobenzylbenzamide (compound 21) was prepared, and 2 ml each thereof was sealed into ampoules and sterilised. This is used as a hypoglycemic injection.

Rising Sun Communications Ltd. Terms and Conditions

Rising Sun Communications Ltd. shall not in any circumstances be liable or responsible for the accuracy or completeness of any translation unless such an undertaking has been given and authorised by Rising Sun Communications Ltd. in writing beforehand. More particularly, Rising Sun Communications Ltd. shall not in any circumstances be liable for any direct, indirect, consequential or financial loss or loss of profit resulting directly or indirectly from the use of any translation or consultation services by the customer.

Rising Sun Communications Ltd. retains the copyright to all of its' translation products unless expressly agreed in writing to the contrary. The original buyer is permitted to reproduce copies of a translation for their own corporate use at the site of purchase, however publication in written or electronic format for resale or other dissemination to a wider audience is strictly forbidden unless by prior written agreement.